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10/517,981	07/14/2005	Michel Maillard	02-415-A1	3761
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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP			EXAMINER	
300 S. WACKER DRIVE			KASTURI, SRIRAM	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/517,981	<b>Applicant(s)</b> MAILLARD ET AL.
	<b>Examiner</b> SRIRAM KASTURI	<b>Art Unit</b> 1612

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on **05-10-08**.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) **1-6, 20, 22, 23, and 25-30** is/are pending in the application.

4a) Of the above claim(s) **7-19, 21 and 24** is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) **1-6, 20, 22, 23, and 25-30** is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date 12-13-04

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_

5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

Claims 1-30 are pending.

***Election/Restrictions***

Applicant's election of Group I, claims 1-6, 20, 22, 23, 25-30 drawn to a method of treating Alzheimer's disease in the reply filed on 5-5-08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In view of applicants arguments claims 2 and 3 are included in the prosecution.

***Specification***

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 6, 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Alzheimer's disease ,

Art Unit: 1612

does not reasonably provide enablement for *preventing* Alzheimer's disease.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) *the nature of the invention*; (2) *the state of the prior art*; (3) *the relative skill of those in the art*; (4) *the predictability or unpredictability of the art*; (5) *the breadth of the claims*; (6) *the amount of direction or guidance presented*; (7) *the presence or absence of working examples*; and (8) *the quantity of experimentation necessary*. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) *The nature of the invention:*

The invention is drawn to a method of treating or *preventing* Alzheimer's disease in a subject in need of such treatment comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. The method of treating Alzheimer's disease by modulating the activity of beta amyloid converting enzyme by administering compound of formula (I). The method of treatment further

Art Unit: 1612

comprising a P-glycoprotein inhibitor and one or more therapeutic agents selected from antioxidant, an anti-inflammatory etc (Claim 20).

*(2) The state of the prior art:*

Prior art at the time of invention suggested the use of rennin inhibitors for treatment of Alzheimer's disease as taught by Amouyel et al (Annals of New York Academy of Sciences, 903:437-441, 2000). Amouyel et al teach presence of renin angiotensin system components in the central nervous system. Brain angiotensin levels influence cognitive processing acquisition and recall of newly learned tasks. Increased levels of angiotensin II induce an inhibitory influence on acquisition by reducing acetylcholine release, this reduction in central cholinergic function is deleterious to cognitive functions. ACE (Angiotensin converting enzyme ) inhibitors which inhibit angiotensin II synthesis will remove inhibitory influence on acetylcholine release (Page 439, 2<sup>nd</sup> paragraph, lines 1-10). Renin controls conversion of Angiotensinogen to Angiotensin I and ACE is involved in conversion of Angiotensin I to Angiotensin II (Page 438, Figure 1). As rennin inhibitors reduce the levels of angiotensin I, there willnot be enough angiotensin I for ACE to act on. Thus renin inhibitors improve cognitive function (Page 439, 2<sup>nd</sup> paragraph, lines 1-10).

Maibaum et al (US5,641,778) teach aromatically substituted omega amino alcanoic acid amides and alcanoic diamides and their use as renin inhibitors. These are compounds of formula (I) as claimed by applicants, that are useful as renin inhibitors and thus useful in treatment.

Art Unit: 1612

Rosenberg et al (US 5,063,208) teach peptidyl aminodiol renin inhibitor compounds useful for treating hypertension congestive heart failure, and glaucoma (Abstract). Their ophthalmic compositions contain antioxidants such as sodium metabisulfite (Col.46, lines 41 and 42). Their teachings include combination of their compounds with calcium channel blockers, verapamil (Col. 47, lines 19-20, 23, 41-43) which is suitable P-glycoprotein inhibitor as indicated by applicants (Specification, Page 35, line 1). Thus Rosenberg et al teach renin inhibitor compositions in combination with antioxidant and P-glycoprotein inhibitor.

*(3) The relative skill of those in the art:*

The relative skill of the those in the art is high. The level of skill of an ordinary person in the art is high, with ordinary artisans having an advanced scientific an/or medical degree (M.D., Ph.D., Pharm.D., or combinations thereof).

*(4) The predictability or unpredictability of the art:*

The unpredictability of the art is high when the claims are drawn to 'preventing' Alzheimer's disease. Applicants indicate in the specification inhibition of beta-secretase mediated cleavage of amyloid precursor protein (APP). The composition is effective in inhibiting the production of beta peptide, thereby they claim prevention of any beta peptide associated pathological condition or disease (Specification, page 20, lines 29-35). However beta deposits or plaque formation is only one of the modes for onset of Alzheimer's disease. There are multiple

Art Unit: 1612

reasons for manifestation of Alzheimer's disease, one of them is missense mutation of amyloid precursor protein (APP) gene, which leads to aggressive form of Alzheimer's disease, as taught by Reiner et al (US PUB 2002/0037843 A1, Page 1, paragraph 0003, lines 5-8).

*(5) The breadth of the claims:*

The claim 1 is very broad. In claim 1 *preventing* Alzheimer's disease is very broad. Applicants are claiming that by using their composition the subjects will be totally prevented of Alzheimer's disease irrespective of the causative reason.

*(6) The amount of direction or guidance presented:*

Though the specification provides guidance about the compound of formula (I), specification does not provide enough guidance about prevention of Alzheimer's disease. In their examples G and H, applicants claim that their composition is expected to demonstrate to slow or stabilize the disease progression (Page 132, lines 17-18 and Page 133, lines 3 and 4). These characteristics are for treating but not for preventing.

(See *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity)). See also *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the

Art Unit: 1612

desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat et al.* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724).

*(7) The presence or absence of working examples:*

Examples provided by applicants, examples G and H (Page 132 and  
133) do not describe the prevention of Alzheimer's disease using their  
composition.

*8) The quantity of experimentation necessary:*

. There is no information about prevention of Alzheimer's disease in their specification. In light of that information it is hard to predict the outcome, which may need undue experimentation to ascertain the prevention of Alzheimer's disease as claimed by applicants.

In conclusion, applicants are enabled only for treating Alzheimer's disease.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Art Unit: 1612

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicants claim a method of treating Alzheimer's disease using aromatically substituted omega amino alcanoic acid amides and diamides.

1. Claims 1-3, 5, 6, 22, 23, and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over teachings of Amouyel et al (Annals of New York Academy of Sciences, 903:437-441, 2000) in view of Maibaum et al (US 5,641,778),

Amouyel et al teach presence of renin angiotensin system components in the central nervous system. Brain angiotensin levels influence cognitive processing acquisition and recall of newly learned tasks. Increased levels of angiotensin II induce an inhibitor influence on acquisition by reducing

Art Unit: 1612

acetylcholine release, this reduction in central cholinergic function is deleterious to cognitive functions. ACE (Angiotensin converting enzyme) inhibitors which inhibit angiotensin II synthesis will remove inhibitory influence on acetylcholine release (Page 439, 2<sup>nd</sup> paragraph, lines 1-10). Renin controls conversion of Angiotensinogen to Angiotensin I and ACE is involved in conversion of Angiotensin I to Angiotensin II (Page 438, Figure 1). As rennin inhibitors reduce the levels of angiotensin I, there will not be enough angiotensin I for ACE to act on. Thus renin inhibitors improve cognitive function (Page 439, 2<sup>nd</sup> paragraph, lines 1-10). However Amouyel et al teachings are silent about compounds.

2. Maibaum et al teach aromatically substituted omega amino alcanoic acid amides and alcanoic diamides and their use as renin inhibitors. They specifically teach compounds which are useful as renin inhibitors and thus useful in treatment of hypertension. Their teachings include the compound of formula I which is shown below. This compound is similar to what applicants are claiming in their claim 1 as the compound of formula (I) and compound of formula (Ia) (Claims 22 and 23) which is an obvious variant of compound of formula (I).

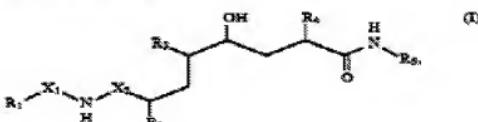
Art Unit: 1612

Maibaum et al compound of formula I is shown above

[57]

**ABSTRACT**

## Compounds of formula I



wherein:

$R_1$  is a  $2-R_A-3-R_B$ -phenyl radical, a  $2-R_A-4-R_C$ -phenyl radical, a  $2-R_A$ -pyridin-3-yl radical, a  $3-R_A$ -pyridin-2-yl radical or a  $1-R_D$ -indol-3-yl radical, wherein one of the radicals  $R_A$  and  $R_B$  is an aliphatic or heterocycloaliphatic-aliphatic radical or free or aliphatically, araphatically or heteroaraphatically esterified hydroxy and the other is hydrogen, an aliphatic radical or free or esterified or amidated carboxy,  $R_C$  is hydrogen, an aliphatic radical, free or aliphatically, araphatically, heteroaraphatically or heteroarylaliphatically esterified hydroxy or an unsubstituted or heteroaliphatically substituted amino group, and  $R_D$  is an aliphatic, araphatic or heteroaliphatic radical, one of the radicals  $X_1$  and  $X_2$  is carbonyl and the other is methylene,  $R_2$  is an aliphatic radical,  $R_3$  is unsubstituted or aliphatically substituted amino,  $R_4$  is an aliphatic or araphatic radical, and  $R_5$  is an aliphatic or cycloaliphatic-aliphatic radical or an optionally hydrogenated and/or oxo-substituted heteroaryl radical or an optionally hydrogenated and/or oxo-substituted heteroaryl or heteroaliphyl radical bonded via a carbon atom, and the salts thereof, have renin-inhibiting properties and can be used as antihypertensive active ingredients of medicaments.

(abstract).

It would have been obvious to one of ordinary skill in the art to use Maibaum's renin inhibitors for the treatment of Alzheimer's disease with a reasonable expectation of success since Amouyel et al teach the involvement of renin in the conversion of angiotensin I to angiotensin II and the suggestion that renin inhibitors improve the cognitive function.

Art Unit: 1612

3. Claims 4 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amouyel et al and Maibaum et al as set forth above, further inview of Rosenberg et al (US 5,063,208) and Chen et al (US Pub 2003/0114373 A1)

The teachings of Amouyel et al and Maibaum et al have been discussed above. Both references lack the teachings of inclusion of either P-glycoprotein inhibitor or antioxidants.

Rosenberg et al (US 5,063,208) teach peptidyl aminodiol renin inhibitor compounds useful for treating hypertension congestive heart failure (Abstract). Their renin inhibitor compound is useful treating vascular diseases (Col. 46, lines 1-5). Their renin compositions contain antioxidants like sodium metabisulfite (Col.46, lines 41 and 42). Their teachings include combination of their compounds with antihypertensive agents like calcium channel blockers, verapamil (Col. 47, lines 19-20, 23, 41-43) which is a suitable P-glycoprotein inhibitor as indicated by applicants (Specification, Page 35, line 1). Thus Rosenberg et al teach renin inhibitor compositions in combination with P-glycoprotein inhibitor and antioxidant as claimed by applicants (Claims 4 and 20 respectively) .

Additionally Chen et al (US Pub 2003/0114373 A1) teach polynucleotides encoding a calpain superfamily CAN-12 protease and variants (Abstract). They teach use of CAN12 for treating hypertension and neurological disorders (Page 17, paragraph 0190 11-14) including Alzheimer's disease (Page 17, paragraph 0192, lines 1-6). Their teachings include use of P-glycoprotein (PGP) antagonists

Art Unit: 1612

in their formulations. PGP is well known for decreasing the efficacy of various drug administrations due to its ability to export intracellular levels of absorbed drug to the cell exterior (Page 159, paragraph 1328, lines 1-8). Whereas use of PGP antagonists (inhibitors) will allow drug to stay in side the cell.

Thus it was obvious to combine P-glycoprotein inhibitor as taught by Chen et al, with Maibaum et al renin inhibitor to have a composition that can be retained in the cell.

Additionally based on Rosenberg et al teachings of compositions containing renin inhibitor, P-glycoprotein inhibitor and antioxidants, it was obvious to prepare a composition containing Maibaum et al renin inhibitor, P-glycoprotein inhibitor like verapamil and an antioxidant like sodium metabisulfite that will retain renin inhibitor inside the cell without further oxidation. Therefore this composition can be used in treating Alzheimer's disease with reasonable expectation of success.

Thus It would have been obvious to one of ordinary skill in the art to use Maibaum' s renin inhibitors in combination with P-glycoprotein inhibitor and antioxidant for the treatment of Alzheimer's disease with a reasonable expectation of success since Amouyel et al teach the involvement of renin in the conversion of angiotensin I to angiotensin II and the suggestion that renin inhibitors improve the cognitive function.

As explained above there is motivation to combine the above teachings to obtain a composition containing Maibaum et al compound , P-glycoprotein

Art Unit: 1612

inhibitor and an antioxidant for treating Alzheimer's disease as claimed by applicants.

Based on the prior art teachings as set forth above in the instant office action there is reasonable expectation of success in preparing a composition that can be used in method of treating Alzheimer's disease.

**Conclusion:**

Claims 1-30 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SRIRAM KASTURI whose telephone number is (571)270-5263. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system.

Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)? If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sriram Kasturi/  
Examiner  
/Gollamudi S Kishore, Ph.D/

Primary Examiner, Art Unit 1612